COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BUSH *et al.*

Appl. No. 09/560,887

Filed: April 28, 2000

For: **Use of Clioquinol for the Therapy of Alzheimer's Disease**

Art Unit: 1615

Examiner: To be assigned

Atty. Docket: 0609.4540002/JAG/HLK

jc857 U.S. PTO
09/972913
10/10/01

Petition Under 37 C.F.R. § 1.47(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

It is hereby petitioned under 37 C.F.R. § 1.47(a) that the Declaration Under 37 C.F.R. § 1.47(a) by Heidi L. Kraus, submitted herewith, be accepted. This Declaration and its Exhibits are attached as Appendix A.

Applicants believe that the facts stated in the Declaration Under 37 C.F.R. § 1.47(a), along with its Exhibits, establish that a *bona fide* attempt was made to present the above-captioned patent application and a declaration for patent application to Mikhal Xilinas, one of the inventors named in the application, and that he has refused to join in the application.

Applicants Ashley I. Bush, Rudolph E. Tanzi, and Robert Cherny respectfully request that a patent be granted in their name in view of the refusal of Mikhal Xilinas to sign the declaration for patent application, as evidenced by the accompanying Declaration Under 37 C.F.R. § 1.47(a).

In accordance with 37 C.F.R. § 1.47(a), applicants state that the last known address of Mikhal Xilinas is **15 Atalante, 145 63 Kisifia, Greece.**

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The fee for this petition is believed to be $130.00 (37 C.F.R. § 1.17(h)). Fee payment is provided by our accompanying check no. **30288**. The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency or credit any overpayment to our Deposit Account No. 19-0036. A duplicate copy of this petition is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Heidi L. Kraus
Attorney for Applicants
Registration No. 43,730

Date: February 5, 2001

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Suite 600
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For: **Use of Clioquinol for the Therapy of Alzheimer's Disease**

Art Unit: 1615

Examiner: To be assigned

Atty. Docket: 0609.4540002/JAG/HLK

Declaration Under 37 C.F.R. § 1.47(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, the undersigned, Heidi L. Kraus, hereby declare and state that:

1. I am attorney for the Massachusetts General Hospital, the assignee of the above-captioned application.

2. I have read and understand 37 C.F.R. §§ 10.18(b) and (c).

3. Mikhal Xilinas has been named as an inventor on the above-captioned application.

4. On January 2, 2001, a Declaration for Patent Application (hereinafter "Declaration"), a copy of the above-captioned application with a copy of the claims as amended, a copy of 37 C.F.R. §§ 10.18(b) and (c), and a cover letter, were sent by Federal Express to both Dr. Mikhal Xilinas and to Mr. Dimitri M. Georgopoulos, previously identified as Dr. Xilinas' attorney. These Federal Express packages were sent to Dr. Xilinas at 15 Atalante, 145 63 Kisifia, Greece, and to Mr. Georgopoulos at, Koniari 45, Athens, GR-114 71. Copies of the documents sent to Dr. Xilinas and Mr. Georgopoulos are attached as Exhibit 1.

5. A Federal Express tracking report indicates that, on January 4, 2001, Dr. Xilinas signed for the Federal Express package sent to his address. This tracking report is attached as Exhibit 2.

6. On January 5, 2001, I received a voicemail message from Dr. Xilinas stating that he received our package, and requesting that I return his call.

7. I spoke to Dr. Xilinas on the telephone on January 16, 2001. During this conversation, he refused to comment on whether he would sign the Declaration and requested that I talk to Mr. Torben Rasmussen, who Dr. Xilinas referred to as his patent counsel.

8. Shortly after speaking to Dr. Xilinas, I called Mr. Rasmussen, but was told he was on vacation.

9. On January 30, 2001, I spoke to Mr. Rasmussen, who identified himself as a European patent agent employed at Internationalt Patent-Bureau in Denmark. Mr. Rasmussen told me that he had advised Dr. Xilinas not to sign the Declaration, but declined to send this statement to us in writing.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Heidi L. Kraus
Attorney for Applicants
Registration No. 43,730

Date: February 8, 2001

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January 2, 2001

WRITER'S DIRECT NUMBER:
(202) 789-5511
INTERNET ADDRESS:
HKRAUS@SKGF.COM

URGENT

Mr. Dimitri M. Georgopoulos
Koniari 45
GR-114 71 Athens
GREECE

Via Federal Express

400-73708084

re: Declaration for U.S. Utility Patent Application No. 09/560,887, Relating to the Use of Clioquinol for the Treatment of Alzheimer's Disease
MGH Ref: 1290.2 CON
GH Ref: VS:SDT:EL:GF35003:GM25371
Our Ref: 0609.4540002/JAG/HLK

Dear Mr. Georgopoulos:

Our law firm handles intellectual property matters for the Massachusetts General Hospital. We have prepared and filed a new patent application at the United States Patent and Trademark Office (USPTO) for the Massachusetts General Hospital, with claims directed to the use of clioquinol for the treatment of Alzheimer's disease. We believe that Dr. Mikhal Xilinas, a client of yours, is a co-inventor of the subject matter of at least one of the claims in the application. A copy of the application and of the presently pending claims is enclosed.

We have also enclosed a "Declaration for Patent Application." The Declaration states that the party signing it is an original, first and joint inventor of the subject matter claimed in the application. In order to complete the formalities for the patent application filed at the USPTO, we must attempt to obtain the signatures of each of the inventors. Therefore, we ask that Dr. Xilinas sign and return this document, if, after careful consideration, he believes himself to be a co-inventor of at least one of the claims of the application.

Please note that every person who signs a document that is submitted to the USPTO makes a certification under USPTO regulation 37 C.F.R. § 10.18(b). A copy of 37 C.F.R. § 10.18(b) and (c) is attached. Therefore, Dr. Xilinas should review this regulation prior to signing the Declaration.

As requested in your letter of July 27, 1999, we are contacting you directly about this matter. However, we have also sent a copy of this letter and the enclosures to Dr. Xilinas directly, to ensure that he receives these documents as soon as possible, as this is an urgent matter.

Instructions on Executing the Declaration

Please have Dr. Xilinas carefully review the Declaration and the information we have entered into it. Please add any missing information using **blue ink**. By "Residence" is meant the city and state of Dr. Xilinas' residence, or if the residence is outside the U.S., the city and country of the residence. The "Post office address" is the full address at which Dr. Xilinas customarily receives mail.

After Dr. Xilinas has reviewed the Declaration, and any necessary corrections have been made, please have him sign and date the document using **blue ink**. His signature and the date should be placed next to the check marks that appear after the phrase "Signature of third inventor."

We request that you or Dr. Xilinas respond to this letter as soon as possible, and preferably by January 10, 2001, regardless of whether Dr. Xilinas agrees to sign the Declaration. The non-extendable deadline for filing the Declaration at the USPTO is February 10, 2001. Therefore, if we do not hear from you or Dr. Xilinas by February 10, 2001, we will file the Declaration without Dr. Xilinas' signature. This action is provided for under USPTO regulations (37 C.F.R. § 1.47).

If you have any questions, or if the documents do not appear to be in order, please contact us immediately.

Very truly yours,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Heidi L. Kraus

HLK/rjv
Encls.
cc: Dr. Mikhal Xilinas (*w/encls., via Federal Express*) 400-73708110
cc: David J. Glass, Ph.D. (*w/ encls. of Assignment and Declaration only, via reg. mail*)
Vivien Santer, Ph.D. (*w/ encls. of Assignment and Declaration only, via Federal Express*)

37 C.F.R. § 10.18(b) and (c): Effect of Signature and Certificate for Correspondence Filed in the Patent and Trademark Office

37 C.F.R. § 10.18(b): By presenting to the Office, (whether by signing, filing, submitting, or later advocating), any paper, the party presenting such paper, whether a practitioner or non-practitioner, is certifying that --

(1) All statements made therein of the party's own knowledge are true, all statements made therein on information and belief are believed to be true, and all statements made therein are made with the knowledge that whoever, in any matter within the jurisdiction of the USPTO, knowingly and willfully falsifies, conceals, or covers up by any trick, scheme, or device a material fact, or makes any false, fictitious or fraudulent statements or representations, or makes or uses any false writing or document knowing the same to contain any false, fictitious or fraudulent statement or entry, shall be subject to the penalties set forth under 18 U.S.C. § 1001, and that violations of this paragraph may jeopardize the validity of the application or document, or the validity or enforceability of any patent, trademark registration, or certificate resulting therefrom; and

(2) To the best of the party's knowledge, information and belief, formed after an inquiry reasonable under the circumstances, that:

(i) The paper is not being presented for any improper purpose, such as to harass someone or to cause unnecessary delay or needless increase in the cost of prosecution before the Office;

(ii) The claims and other legal contentions therein are warranted by existing law or by a nonfrivolous argument for the extension, modification, or reversal of existing law or the establishment of new law;

(iii) The allegations and other factual contentions have evidentiary support or, if specifically so identified, are likely to have evidentiary support after a reasonable opportunity for further investigation or discovery; and

(iv) The denials of factual contentions are warranted on the evidence, or if specifically so identified, are reasonably based on a lack of information or belief.

37 C.F.R. § 10.18(c): Violations of paragraph (b)(1), by a practitioner or a non-practitioner, may jeopardize the validity of the application or document, or the validity or enforceability of any patent, trademark registration, or certificate resulting therefrom. Violations of any of paragraphs (b)(2)(i) through (iv) of this section are, after notice and reasonable opportunity to respond, subject to such sanctions as deemed appropriate by the Commissioner, or the Commissioner's designee, which may include, but are not limited to, any combination of:

(1) Holding certain facts to have been established;
(2) Returning papers;
(3) Precluding a party from filing a paper, or presenting or contesting an issue;
(4) Imposing a monetary sanction;
(5) Requiring a terminal disclaimer for the period of the delay; or
(6) Terminating the proceedings in the Patent and Trademark Office.

Declaration for Patent Application

Docket Number: 0609.4540003/JAG/FRC

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled: _ **Use of Clioquinol for the Therapy of Alzheimer's Disease**,

the specification of which is attached hereto unless the following box is checked:

■ was filed on October 10, 2001;
as United States Application Number 09/972,913; and
was amended on October 10, 2001 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56, including for continuation-in-part applications, material information that became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or (f), or § 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or § 365(a) of any PCT international application, which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Claimed
_____ (Application No.)	_____ (Country)	_____ (Day/Month/Year Filed)	☐ Yes ☐ No
_____ (Application No.)	_____ (Country)	_____ (Day/Month/Year Filed)	☐ Yes ☐ No

Send Correspondence to:

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934

Direct Telephone Calls to:

(202) 371-2600

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor	Ashley I. Bush
Signature of sole or first inventor	Date
Residence	Sommerville, MA
Citizenship	Australia
Mailing Address	91 Summer Street, Apt. 3 Sommerville, MA 02143

Full name of second inventor	Rudolph E. Tanzi
Signature of second inventor	Date
Residence	Hull, MA
Citizenship	USA
Mailing Address	3 Oceanside Hull, MA 02045

Full name of third inventor	Mikhal Xilinas
Signature of third inventor ✓	✓ Date
Residence	Athens, Greece
Citizenship	Greece
Mailing Address	15 Atalante 145 63 Kisifia, Greece

Full name of fourth inventor	Robert Cherny
Signature of fourth inventor	Date
Residence	Melbourne, Australia
Citizenship	Australia
Mailing Address	33 Davey Avenue Brighton East, Victoria Australia

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(Supply similar information and signature for subsequent joint inventors, if any)

Claims Presently Pending in Application No. 09/560,887

Claim 2 has been canceled. Claims 1 and 3-11 are still pending in the Application. The following new claims, 12-46, have been added:

12. A method of treating a subject having or suspected of having Alzheimer's disease comprising administering to the subject an amount of clioquinol effective to treat Alzheimer's disease.

13. The method according to claim 12, wherein the clioquinol is (a) administered for one to 21 days, followed by (b) a period of one to four weeks during which clioquinol is not administered.

14. A method of treating a subject having or suspected of having Alzheimer's disease comprising administering to the subject an amount of clioquinol effective to increase the solubility of amyloid-beta in the cerebrospinal fluid of said subject.

15. A method of treating a subject having or suspected of having Alzheimer's disease comprising administering to the subject (a) an amount of clioquinol effective to treat or prevent Alzheimer's disease, and (b) an amount of vitamin B_{12}.

16. The method according to claim 15 wherein the amount of vitamin B_{12} is effective to inhibit a detrimental side effect of clioquinol administration.

17. The method according to claim 15 wherein a pharmaceutical composition comprising clioquinol is administered for one to 21 days, followed by a period of one to four weeks during which a pharmaceutical composition comprising vitamin B_{12} is administered and clioquinol is not administered.

18. The method according to claim 15 wherein the clioquinol and vitamin B_{12} are administered sequentially.

19. The method according to claim 15 wherein the clioquinol and vitamin B_{12} are administered substantially simultaneously.

20. The method according to claim 16 wherein a pharmaceutical composition comprising clioquinol is administered for one to 21 days, followed by a period of one to four weeks during which a pharmaceutical composition comprising vitamin B_{12} is administered and clioquinol is not administered.

21. The method according to claim 12, 14 or 15, wherein the subject is human.

22. The method according to claim 12 or 15, wherein the clioquinol is administered in an amount of 5-10 mg/kg body weight one to four times daily.

23. The method according to claim 12, wherein trace metals are administered together with or subsequent to the administration of clioquinol.

24. The method according to claim 12 or 15, wherein the clioquinol is administered intermittently.

25. The method according to claim 12, wherein the clioquinol is administered for up to ten years.

26. The method according to claim 12 or 15, wherein the clioquinol is formulated for oral administration.

27. The method according to claim 12 or 15, wherein the clioquinol is formulated for parenteral or intradermal administration.

28. The method according to claim 12 or 15, wherein the vitamin B_{12} is formulated for intramuscular administration.

29. The method according to claim 12 or 15, wherein the vitamin B_{12} is formulated for oral administration.

30. The method according to claim 15, 16 or 17, wherein the clioquinol and vitamin B_{12} are each purified.

31. A pharmaceutical composition comprising an amount of clioquinol effective to treat Alzheimer's disease, and vitamin B_{12}.

32. The pharmaceutical composition according to claim 31, which further comprises a pharmaceutically acceptable carrier.

33. The pharmaceutical composition according to claim 31, wherein the amount of clioquinol is 5-10 mg/kg body weight.

34. The pharmaceutical composition according to claim 31, wherein the amount of vitamin B_{12} is 7-10 mg/kg bodyweight.

35. The pharmaceutical composition according to claim 31, wherein the amount of vitamin B_{12} is 70-100 μg/kg bodyweight.

36. The pharmaceutical composition according to claim 31, wherein the composition is formulated for parenteral or intradermal administration.

37. The pharmaceutical composition according to claim 31, wherein the composition is formulated for oral administration.

38. The pharmaceutical composition according to claim 31 or 32, wherein the clioquinol and vitamin B_{12} are each purified.

39. A pharmaceutical composition comprising a therapeutically effective amount of clioquinol and vitamin B_{12}.

40. The pharmaceutical composition according to claim 39, which further comprises a pharmaceutically acceptable carrier.

41. The pharmaceutical composition according to claim 39, wherein the amount of clioquinol is 5-10 mg/kg body weight.

42. The pharmaceutical composition according to claim 39, wherein the amount of vitamin B_{12} is 7-10 mg/kg bodyweight.

43. The pharmaceutical composition according to claim 39, wherein the amount of vitamin B_{12} is 70-100 μg/kg bodyweight.

44. The pharmaceutical composition according to claim 39, wherein the composition is formulated for parenteral or intradermal administration.

45. The pharmaceutical composition according to claim 39, wherein the composition is formulated for oral administration.

46. The pharmaceutical composition according to claim 39 or 40, wherein the clioquinol and vitamin B_{12} are each purified.

Exhibit 2 - Tracking Report

FEDERAL EXPRESS
FowerShip 3 TRACK REPORT
LINK0371

Tracking # 408737088110 Svc: FP
Delivered
ATHENS GR 01/04 13:55
Package Status Exception
ATHENS GR 01/04 07:55
Package Left FedEx Ramp
STANSTED GB 01/03 19:25
Pkg Left FedEx Sort Facility
MEMPHIS TN 01/03 01:38
Int'l Pkg Manifest Created
MEMPHIS TN 01/02 23:54
Package Left FedEx Ramp
DULLES VA 01/02 23:34
Left FedEx Origin Location
WASHINGTON DC 01/02 21:22
Picked up
WASHINGTON DC 01/02 21:07

Delivered to..:
Recept/Frnt desk
Signed for by.:
,.XILINAS
Delivery time.:
13:55
Stat Exception:
COMM/DUTBL rcvd at entry port